Remarks

Prior to this amendment, claims 1-35 were pending in this application, of which claims 13-18 were withdrawn. Claims 1, 19, 29, and 33 are amended herein. Claims 13-18 are canceled. Support for the amendment of claims 1, 19, 29, and 33 can be found in the specification at least at page 10, lines 10-20; page 21, lines 10-19; page 24, lines 5-10; and page 55, lines 4-6. Support for the amendment of claims 1 and 29 can also be found in the specification at least at page 38, lines 2-5. Additional support for the amendment of claim 33 can be found in the specification at page 40, lines 5-9.

No new matter has been added by these amendments. Unless specifically stated otherwise, none of these amendments are intended to limit the scope of any claim. Applicants reserve the right to prosecute any removed subject matter in a continuation application. After entry of this amendment, **claims 1-12 and 19-35 are pending in this application**. Reconsideration of the pending claims is respectfully requested.

Information Disclosure Statements

Applicants thank the Examiner for considering the references cited in the Information Disclosure Statements submitted on December 7, 2004, January 4, 2005, May 18, 2006, and September 29, 2006.

Restriction Requirement

Applicants acknowledge that the election of Group I (claims 1-12 and 19-35) is made final and that claims 13-18 are withdrawn. In addition, Applicants acknowledge that the species election of T cell chemotaxis is made final.

Claim Objections

Claims 20 and 21 are objected to as allegedly being in improper dependent form for failing to further limit the subject matter of a previous claim. Claim 20 is amended to be dependent from claim 19. As amended claim 20 is directed to an embodiment encompassed by claim 19, claim 20 further limits the subject matter of the previous claim. Similarly, claim 20 is directed to a specific embodiment encompassed by claim 20 and therefore is also further

limiting. In light of the above discussion and amendment of claim 20, Applicants respectfully request that the objection of claims 20 and 21 be withdrawn.

Claim Rejections Under 35 U.S.C. §112, second paragraph

Claims 1-35 are rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection.

Claim 1

Claim 1 is rejected for allegedly being vague and indefinite because the claim "does not convey that the substitution is directly related to the increased activity or stability." Solely to advance prosecution in this case, claim 1 is amended to recite "wherein the tryptophan-substituted or phenylalanine-substituted polypeptide has increased antimicrobial activity or polypeptide stability," as suggested by the examiner. In light of the amendment of claim 1, Applicants submit that this claim is clear and definite and respectfully request that this rejection be withdrawn.

Claims 1, 19, and 29

Claims 1, 19, and 29 are rejected for allegedly not being clear as to what type of increased activity or stability the claim refers to. Solely to advance prosecution in this case, claims 1, 19, and 29 are amended to recite that the increased activity or stability is "increased antimicrobial activity or polypeptide stability." In light of the amendment of claims 1, 19, and 29, Applicants submit that these claims are clear and definite and respectfully request that this rejection be withdrawn.

Claims 1, 13, 15, 19, 29, and 33

Claims 1, 13, 15, 19, 29, and 33 are rejected for allegedly being indefinite for reciting the phrase "capable of being ADP-ribosylated." Claims 13-18 are canceled herein, rendering the rejection of claims 13 and 15 moot. Solely to advance prosecution in this case, claims 1, 19, 29, and 33 are amended to remove the phrase "capable of being ADP-ribosylated." In light of the

amendment of claims 1, 19, 29, and 33, Applicants submit that these claims are clear and definite and respectfully request that this rejection be withdrawn.

As discussed above, claims 1, 19, 29, and 33 are amended. Claims 2-12, 20-28, 30-32, and 34-35 depend (directly or indirectly) from these claims and incorporate all of the limitations thereof. In light of the above discussion and amendments, Applicants respectfully submit that the current claims are clear and definite and request that the rejection of the claims under 35 U.S.C. §112, second paragraph, be withdrawn.

Claim Rejections Under 35 U.S.C. §112, first paragraph (enablement)

Claims 1-12 and 33-34 are rejected under 35 U.S.C. §112, first paragraph, as allegedly the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with the claims. Specifically, the Office alleges that claim 1 is not enabled for "ANY protein with an increased activity or stability comprising replacing arginine residue with a tryptophan or phenylalanine residue" (Office action at page 7). In addition, the Office alleges that claims 33-34 are not enabled for a "method of increasing an immune response in a subject by administering the substituted amino acid of defensin polypeptide wherein the subject has *any* immune disorder" (Office action at page 6). Applicants respectfully disagree with this rejection.

The Federal Circuit has repeatedly stated that enablement is not precluded by the necessity for some experimentation, so long as the experimentation is not undue. *In re Wands* 8 USPQ2d 1400 (Fed. Cir. 1988). A considerable amount of experimentation is permissible, if it is **merely routine**, or if the specification provides a reasonable amount of guidance in which the experimentation should proceed. *Id.* Applicants submit that any experimentation would be routine and the present application provides the guidance necessary to carry out the claimed methods.

For example, with regard to claim 1, the Office alleges that "[g]iven the lack of guidance contained in the specification regarding the location of acceptable amino acid substitutions, and their specific location within the polypeptide relating to a specific activity (e.g. increased

neutrophil recruitment, etc.) one of skill in the art could not make or use the broadly claimed invention without undue experimentation" (Office action, page 8). Applicants disagree. First, the steps required to make the tryptophan-substituted or phenylalanine-substituted polypeptides are well known to those of skill in the art. For example, the use of automated peptide synthesizers was well known to those of skill in the art at the time the subject application was filed and methods to generate synthetic polypeptides are described in the subject application, for example at page 36, lines 20-30. Thus, it would merely be **routine** to make the tryptophan-substituted or phenylalanine-substituted polypeptides. Moreover, it would be routine to analyze polypeptide sequences using algorithms widely available at the time the application was filed, including BLAST (Altschul *et al.,* 1990, *J. Mol. Biol.* 215:403-410), PFAM (Bateman *et al.,* 1999, *Nucleic Acids Res.* 27:260-262), PSORT (Nakai K, and Horton P, 1999, *Trends Biochem. Sci.* 24:34-6), and/or CLUSTAL (Thompson JD *et al.,* 1994, *Nucleic Acids Res.* 22:4673-4680) in order to identify conserved domains in the polypeptides to be substituted. One of skill in the art could use this information determine where to make arginine-to-tryptophan or arginine-to-phenylalanine substitutions.

Second, the specification teaches methods for testing a tryptophan-substituted or phenylalanine-substituted polypeptide to determine if it has increased antimicrobial activity or polypeptide stability (specification at page 37, line 1 through page 38, line 25). Based on the teachings of the specification, examples directed to assessing the activity or stability of particular tryptophan-substituted or phenylalanine-substituted polypeptides are provided (see, for example, the specification at page 50, lines 21-28; page 54, lines 1-14; and page 54, line 29 through page 56, line 32). Such methods include assays that measure ADP-ribosylation, cytotoxicity, interleukin-8 release, and chemotaxis.

With regard to claims 33 and 34, the Office alleges that "the claim language is so broad that it encompasses modifying immune response in ANY subject with ANY immune disorder" (Office action at page 8). Applicants disagree. However, solely to advance prosecution in this case, claim 33 is amended to recite "increasing an antimicrobial immune response in a subject infected with or at risk of being infected with a microbe." The specification clearly teaches administering a therapeutically effective amount of a tryptophan-substituted or phenylalanine-

substituted defensin molecule to subjects who are infected with or at risk of being infected with a microbe, including how to prepare, dose, and administer the therapeutically effective composition (specification at page 41, line 23 through page 44, line 4).

Thus, based on the teachings of the specification and the knowledge of one of skill in the art, it would be simply a matter of **routine** skill to carry out the claimed methods and undue experimentation would not be required. Applicants submit that amended claims 1-12 and 33-34 are fully enabled by the specification. Applicants request that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

Claim Rejections Under 35 U.S.C. §102

Claims 1, 2, 5, 7-9, 19-22, and 24 are rejected as allegedly anticipated by Svendsen *et al.* (U.S. Patent Publication No. US 2003/0148936) under 35 U.S.C. §102(b). Applicants respectfully traverse this rejection.

Applicants respectfully submit that the Office has misinterpreted Svendsen *et al.* For example, the Office action states that "Svendsen *et al.* further teach that peptides encorporating (sic) lipophilic amino acid[s] such as tryptophan and phenylalanine will preferably exhibit an enhanced cytotoxic effect against bacterial or tumor cells (p1, [0008-0010])" (Office action at page 10). Applicants disagree. In fact, paragraph [0010] states that "[p]eptides incorporating a **non-genetic** bulky and lipophilic amino acid will preferably exhibit an enhanced cytotoxic effect against bacterial or tumor cells" (emphasis added). Svendsen *et al.* specifically defines a non-genetic bulky and lipophilic amino acid as "any amino acid or amino acid derivative, which may be naturally occurring, but **not one of the 20 standard genetically coded amino acids**" (emphasis added; paragraph [0011]). Consequently, Svendsen *et al.* at paragraph [0010] was not referring to tryptophan and phenylalanine, as the Office alleges.

The Office also alleges that Svendsen *et al.* teaches "that increased bioactivity was as a result of a serendipitous transfer of Pmc from arginine to tryptophan, amino acids such as Trp, which carry the protecting group can be synthesized directly and incorporated into the peptide (p 3, [0018])" (Office action at page 10). Applicants submit that paragraph [0018] of Svendsen *et*

al. in fact teaches the use of a chemical protecting group to increase the bulk and lipophilicity of a residue, which in turn can increase the bioactivity of a peptide (see also Svendsen *et al.* at paragraph [0017]). This is in direct contrast with the claimed invention, which only requires the substitution of an arginine residue with an unmodified tryptophan or phenylalanine residue. Thus, paragraph [0017] of Svendsen *et al.* is not relevant to the claimed invention.

The Office further alleges that Svendsen *et al.* teaches the "substitution for the native peptide and a number of modified peptides wherein single amino acid substitutions for tryptophan or phenylalanine at positions 16 or 19 have been made, with a resulting increase in antibacterial activity (p 21, [0280], and table 7)" (Office action at page 11). However, neither paragraph [0280] nor table 7 teach that the substitution of an arginine residue, specifically, with a tryptophan or phenylalanine results in an increase in antibacterial activity, as required by the claims. The Office further points to paragraphs [0001], [0002], [0062], and [0031] that Svendsen *et al.* allegedly teaches the claimed invention. However, these paragraphs only make broad statements that the modification of proteins can alter bioactivity and do not specifically teach the claimed invention.

Applicants also point out that Svendsen *et al.* does not specifically teach comparing the antimicrobial activity or polypeptide stability of a polypeptide of interest with a tryptophan-substituted or phenylalanine-substituted polypeptide, wherein the tryptophan-substituted or phenylalanine-substituted polypeptide has:

(i) increased antimicrobial activity or polypeptide stability compared to the polypeptide of interest, and

(ii) similar antimicrobial activity or polypeptide stability to the polypeptide of interest, wherein the arginine residue is ADP-ribosylated,

as required by the present claims.

Based on the above discussion, Svendsen *et al.* does not meet every limitation of the current claims. Accordingly, Svendsen *et al.* does not anticipate the claimed invention. Applicants respectfully request that this rejection of claims 1, 2, 5, 7-9, 19-22, and 24 be withdrawn in light of the above arguments and amendments to the claims.

Claim Rejections Under 35 U.S.C. §103

Claims 1-3, 5-9, and 19-35 are rejected as allegedly unpatentable under 35 U.S.C. §103 over Svendsen *et al.* in view of Paone *et al.* (Proc. Natl. Acad. Sci., 99:8231-8235, 2002). Applicants respectfully traverse this rejection.

As discussed above, Svendsen *et al.* does not teach every limit of the current claims. Paone *et al.* discloses that ADP-ribosylation of defensins alters its biological properties. However, as with Svendsen *et al.*, Paone *et al.* does not specifically teach comparing the antimicrobial activity or polypeptide stability of a polypeptide of interest with a tryptophan-substituted or phenylalanine-substituted polypeptide, wherein the tryptophan-substituted or phenylalanine-substituted polypeptide has:

(i) increased antimicrobial activity or polypeptide stability compared to the polypeptide of interest, and

(ii) similar antimicrobial activity or polypeptide stability to the polypeptide of interest, wherein the arginine residue is ADP-ribosylated,

as required by the present claims.

Applicants submit that Paone *et al.* does not overcome the deficiency of Svendsen *et al.* Thus, claims 1-3, 5-9, and 19-35 are both novel and non-obvious over Paone *et al.* in combination with Svendsen *et al.* Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-3, 5-9, and 19-35.

Conclusion

Based on the foregoing amendments and arguments, the claims are in condition for allowance and notification to this effect is requested. If for any reason the Examiner believes that a telephone conference would expedite allowance of the claims, please telephone the undersigned at the number listed below.

Respectfully submitted,

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